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Influence of Essential Amino Acids on the Synthesis of Polyproteins of the SARS-CoV-2 Virus in the COVID-19 Pathogenesis

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ABSTRACT

Introduction. Diet is a critical factor in the development of viral pathogenesis. Previously it was shown that a high intake of proteins correlated directly with dangerous outcomes of SARS-CoV-2 infection. It is necessary to analyze the biochemistry of the metabolic relations of the host and pathogen to explain the contribution of proteins in the development of COVID-19.

Purpose. Identify a risk factor influencing the development of the COVID-19 disease. Compare the amino acid composition of animal and plant proteins with non-structural polyproteins of the SARS-CoV-2 virus. Analyze the impact of dietary essential amino acids (EAAs) in the COVID-19 infectious disease.

Materials and Methods. The scientific data and information needed for this analysis were found in publications and media available on the Internet, as well as taken from statistical databases. Statistical samples were formed from sources and facts available on the Internet. Amino acid sequences of proteins were obtained from databases (https://www.ncbi.nlm.nih.gov/, https://www.uniprot.org/uniprot/).

Results and Discussion. Analysis of statistical data and assessment of nutritional factors during the development of the 22-month pandemic in 20 countries indicated that the outcomes of COVID-19 disease were worsened by excessive consumption of animal proteins. The numbers of reported cases of SARS-CoV-2 virus (RPr) infection and deaths (IFR) from the COVID-19 disease per one thousand inhabitants were significantly lower in regions that predominantly consumed plant-based foods with minimal EAAs. A positive relationship was found between the pathogenicity of SARS-CoV-2 and the amount of animal protein ingested, with correlation coefficients $r = 0.83$ for RPr and $r = 0.61$ for IFR. Human Coronaviruses are composed of higher proportion of EAAs than cellular organisms. Edible plant proteins contain 2-3 times less leucine, lysine, and especially threonine and valine (LKTV) than SARS-CoV-2 polypeptides. Optimal synthesis of the SARS-CoV-2 virus Pp1a and Pp1ab polyproteins requires a rapidly large amount of these four EAAs.

Conclusions. A deficiency of EAAs, especially free valine, and threonine, could suppress the early translation of SARS-CoV-2 nonstructural polyproteins. It was concluded that a diet low in EAAs and especially LKTV may prevent rapid, highly productive viral replication and pathogenic development of COVID-19.

KEYWORDS

animal proteins; coronavirus SARS-CoV-2; COVID-19; diet; essential amino acids; infection; pandemic; pathogenesis; polyprotein; protein synthesis; risk factor

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Влияние незаменимых аминокислот на синтез полипротеинов вируса SARS-CoV-2 в патогенезе COVID-19

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АННОТАЦИЯ

Введение. Диета является решающим фактором в развитии вирусного патогенеза. Предварительно было показано, что высокое потребление животных белков напрямую коррелирует с опасными исходами инфекции SARS-CoV-2. Анализ биохимии метаболических отношений хозяина и возбудителя необходим для выяснения роли животных белков в развитии COVID-19.

Цель. Выявить диетический фактор, влияющий критически на развитие заболевания COVID-19. Сравнить аминокислотный состав животных и растительных белков с неструктурными полипротеинами вируса SARS-CoV-2. Проанализировать влияние незаменимых аминокислот (EAA) на развитие инфекционного заболевания COVID-19.

Материалы и методы. Данные и информация, необходимые для этого анализа, были найдены в публикациях и СМИ, доступных в Интернете, а также взяты из статистических баз данных. Статистические выборки формировались из источников и фактов, доступных в Интернете. Аминокислотные последовательности белков были получены из баз данных (https://www.ncbi.nlm.nih.gov/, https://www.uniprot.org/uniprot/).

Результаты и обсуждение. Анализ статистических данных и оценка факторов питания в период развития 22-месячной пандемии в 20 странах, с наибольшим числом инфицированных пациентов, показали, что исход заболевания COVID-19 усугублялся избыточным потреблением белков животного происхождения. Количество зарегистрированных случаев заражения вирусом SARS-CoV-2 (RPr) и смертности (IFR) от болезни COVID-19 на тысячу жителей было значительно ниже в регионах, где потреблялась преимущественно растительная пища с минимальным содержанием EAA. Выявлена положительная связь между патогенностью SARS-CoV-2 и количеством поступающих в организм животных белков с коэффициентами корреляции r = 0,83 для RPr и r = 0,61 для IFR. Коронавирусы человека содержат гораздо больше EAA, чем клеточные организмы. Съедобные растительные белки содержат в 2-3 раза меньше лейцина, лизина и особенно треонина и валина (LKTV), чем полипептиды SARS-CoV-2. Для оптимального синтеза полипротеинов Pp1a и Pp1ab вируса SARS-CoV-2 требуется своевременное поступление большого количества этих четырех EAA.

Выводы. Дефицит EAA, особенно свободного валина и треонина, может подавлять раннюю трансляцию белков Pp1a и Pp1ab вируса SARS-CoV-2. Предполагается, что диета с низким содержанием EAA и особенно LKTV может предотвратить быструю, высокопродуктивную репликацию вируса и патогенное развитие COVID-19.

КЛЮЧЕВЫЕ СЛОВА:
животные белки; коронавирус SARS-CoV-2; COVID-19; диета; незаменимые аминокислоты; инфекционное заболевание; пандемия; патогенез; полипротеин; синтез белка; фактор риска

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ABBREVIATIONS: AAs — Amino Acids, ACE2 — membrane bound Angiotensin-Converting Enzyme 2, BCAA — Branched-Chain Amino Acid, ßCoV- Betacoronavirus, EAAs — Essential Amino Acids, FAAs –Free Amino acids, gRNA — genomic RNA, HCoV — Human Coronaviruses, IFR — Infection Fatality Rate, Km — Michaelis-Menten coefficient, LAAs — Limited Amino Acids, LKTV — Leucine+Lysine+Threonine+Valine, NTP — nucleoside triphosphate, Pp1a and Pp1ab — Polyproteins, PT2 — Pneumocytes Type 2, rER — rough Endoplasmic Reticulum, RPr — Rate of Prevalence, SARS — Severe Acute Respiratory Syndrome, cSME — Spike, Membrane and Envelope proteins-lipid complex, WHO — World Health Organization.

INTRODUCTION

Coronavirus SARS-CoV-2 was discovered three years ago, and the COVID-19 pandemic caused by it hindered almost all aspects of human activity[1](CDC, 2022). Unfortunately, there is no etiotropic or highly effective drug blocking the replication cycle of the SARS-CoV-2 virus yet, and a radical decrease in infection dynamics has not been observed globally (Worldometers, 2022; Mei & Tan, 2021; Yapasert et al., 2021). Humanity will fight the SARS-CoV-2 virus infection and the consequences of the pandemic for another year or more in various ways. Numerous studies have shown that social isolation, sanitary measures, and vaccination help fight the virus. Comorbidities, advanced age, obesity, or severe malnutrition are risk factors for the severity of COVID-19[2] (CDC, 2022).

The importance of nutrition in the outcome of SARS-CoV-2 infections has been explored in dozens of research programs across countries and populations. Numerous studies on the effect of diet on COVID-19 outcomes have been published, which allowed data to be processed and analyzed in systematic reviews (Allard et al., 2020; Bedock et al., 2021; Clemente-Suarez et al., 2021; James et al., 2021; Mentella et al., 2021; Mechanick et al., 2021; Morais et al., 2021; Mortaz et al., 2021). Diet type has also been shown to be the critical socioeconomic factor for the virus´s pathogenic development. It was demonstrated that the consumption of excess fat, sugar, and protein linearly correlated with the severity of COVID-19 disease and mortality (Ponomarenko, 2022; Ponomarenko, 2023). It has been shown that adequate consumption of total and plant proteins correlated with a low incidence of negative manifestations of the pathogenesis of the SARS-CoV-2 virus (Ponomarenko, 2022; Kim et al., 2021). Excessive consumption of animal proteins is a serious factor in many health problems (Wu, 2016) and a risk of severe development of SARS-CoV-2 as well (Ponomarenko, 2022).

Optimal interaction with its host is fundamental for a successful viral replication cycle. The development of COVID-19 infection depends on the level of biochemical interactions between the virus and the host. The pathogen has been shown to destabilize proteostasis and amino acid homeostasis (Aller et al., 2018; Bojkova et al., 2020; Delattre et al., 2020; Mussap &Fanos, 2021; Paez-Franco et al., 2021; Wu et al., 2021). Viruses use intracellular mechanisms and building resources for productive replication. If the body is not able to supply sufficient nutrients to synthesize the necessary viral proteins, pathogen replication should slow down or be interrupted. The amount of the synthesized viral proteins after the invasion of the pathogen into the cell increases successively passing through the lag phase, the rapid growth phase, and the exponential phase (Bojkova et al., 2020; Wu et al., 2021; Cheemarla et al., 2021; Pyke et al., 2021). In the rapid growth phase and especially in the exponential phase, viral replication requires high availability of substrates for biosynthetic reactions. The consequence of EAA availability for the synthesis of SARS-CoV-2 proteins has not been studied previously. For a practical understanding of the significance of limiting EAAs in the pathogenesis of COVID-19, it should be compared the biochemical characteristics of the virus and the host.

MATERIAL AND METHODS

For the study, required information was systematically searched on the Internet using single keywords and combination thereof. Data from 20 countries with the highest reported number of cases were analyzed. AA sequences of virus proteins were acquired from databases (https://www.ncbi.nlm.nih.gov/, https://www.uniprot.org/uniprot/). Most of the statistics were obtained from the following well known and reliable databases: https://www.who.int; https://www.worldometers.info; http://www.fao.org; https://ourworldindata.org; https://databank.worldbank.org; https://www.imf.org. The rate of prevalence (RPr) or infection fatality rate (IFR) of the virus were calculated as a ratio between quantities of total cases and population. Case fatality rate (CFR) was the ratio between total COVID-19 deaths and total registered infection cases in percentage. The relationship between statistical data was estimated as a Pearson correlation coefficient (r).

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[1] World Health Organization. https://www.who.int

[2] там же

RESULTS AND DISCUSSION

Characteristics of the development of the COVID-19 pandemic over two years

The pathogenic SARS-CoV-2 virus was discovered three years ago. In around 700 days (Monday, January 31, 2022), after the announcement of the COVID-19 pandemic by WHO, there were about 380 million patients globally infected with the SARS-CoV-2 virus: approximately 5 % of the world's population. To date, the current COVID-19 pandemic has entered its sixth wave of infections and deaths (Worldometers, 2022). WHO experts have identified three main groups of patients infected with the virus, depending on the development of the disease[3](CDC, 2022). The largest group of patients had the infection with mild or no symptoms; the next group included patients with severe disease, and 5 % of COVID-19 patients developed to a critical phase with a high mortality rate. To date, about 300 Mio people (79 % of infected people) have recovered from the disease and approximately 5.7 Mio COVID-patients (1.5 %) died (Worldometers, 2022).

Data on the consequences of the infectious disease COVID-19 vary significantly between different continents, states, and even distinct regions in the same country[4] (CDC, 2022; Worldometers, 2022; Ponomarenko, 2022, Ponomarenko, 2023). Three countries: the United States of America (USA), India, and Brazil, have recorded the most infections and deaths from COVID-19. These three countries were home to 38 % of the globally infected and 37 % of all deaths. With 22.8 %, the USA had the highest number of registered infections per capita (RPr) of these three countries, and the USA also had the highest mortality (IFR): 0.27 %. On the other hand, in some European countries, RPr exceeded 35 %, which was 6–7 times higher than the global average (Worldometers). In Peru, the IFR was roughly an order of magnitude higher than the global average (0,6 % compared to 0.07 %). The emergence of new variants of the virus poses a risk for the further development of the epidemic; an increase in COVID-19 cases and deaths is possible in the coming months if drastic measures would not be taken to combat the SARS-CoV-2 virus.

Related molecular biological characteristics of the SARS-CoV-2 virus

The SARS-CoV-2 virus belongs to the Betacoronavirus (ßCoV) genus. ßCoV are the largest and most developed RNA viruses; their genome type is designated NSss+RNA since they have an non-segmented single-stranded positive-sense RNA. Coronaviruses that cause disease in humans are referred to as HCoV. The linear genomic RNA (gRNA) of ßCoV is about 30 kb in size and protected by a developed spiral capsid (Abdelrahman &Wang, 2020; Hu et al., 2021; To et al., 2021; V´kovski et al., 2021).

The genetics, structure, and function of SARS-CoV-2 proteins have been well studied and discussed in many publications, as well as detailed in several reviews (Abdelrahman &Wang, 2020; Hu et al., 2021; To et al., 2021; V´kovski et al., 2021;Yadav et al., 2021; Yoshimoto, 2020). Large databases of the sequence, structure, and function of ßCoV proteins have been created (NCBI, 2022; UniProt, 2022). It was believed that few of the viral proteins can be the subject of vaccines or targeted inhibitors (Yapasert et al., 2021; Yadav et al., 2021; Yoshimoto, 2020).

The virus has no storage proteins, so all proteins are needed for its rapid reproduction. The genome of Coronaviruses encodes the synthesis of structural and functional polypeptides (Hu et al., 2021; To et al., 2021; V´kovski et al., 2021; Yadav et al., 2021; Yoshimoto, 2020). The functional open reading frame ORF1ab is located in the 5'-genomic region from 268 to 21555 nucleotides of the SARS-CoV-2 virus (V´kovski et al., 2021; Yadav et al., 2021; Yoshimoto, 2020) and contains 16 nsp genes encoding the same amount of non-structural proteins (NSPs). The ORF1ab makes up approximately two-thirds of the viral genome. It encodes the production of two, primarily translated, polyproteins Pp1a and Pp1ab (V´kovski et al., 2021;Yadav et al., 2021; Yoshimoto, 2020; NCBI, 2022; UniProt, 2022; Finkel et al., 2021). These two polypeptides are synthesized directly upon invasion by using gRNA as a template. The Pp1a polypeptide is expressed 1.4–2.2 times faster than Pp1ab (V´kovski et al., 2021;Yadav et al., 2021). This is a co-translational result of a programmed -1 ribosome frameshift common to Coronaviruses (Bhatt et al., 2021). Eleven NSPs, from the nsp1 to nsp11 genes, are released from the Pp1a polyprotein, and fifteen protein types: nsp1–10 plus nsp12–16 are released from Pp1ab after post-translational proteolytic cleavage (V´kovski et al., 2021; Yoshimoto 2020).

As in other HCoVs, four genes encoding structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N) are located in the 5' to 3' direction of the remaining third of the SARS-CoV-2 genome. These genes border on a variable number of accessory proteins (Hu et al., 2021; To et al., 2021; V´kovski et al., 2021;Yadav et al., 2021; Yoshimoto 2020). The intensively studied spike protein is the largest structural polypeptide containing 1273 amino acid residues (Yadav et al., 2021; Yoshimoto 2020; NCBI, 2022; UniProt, 2022). Spike polypeptides are synthesized at a higher rate than other structural proteins (Finkel et al., 2021) and form glycosylated trimers after folding. They, in combination with the M and E proteins, are released from rER and then form a specific protein-lipid complex (cSME) with the membranes of the Golgi apparatus (Yadav et al., 2021; Yoshimoto, 2020). N-proteins

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[3] World Health Organization. https://www.who.int

[4] там же

associate with newly synthesized gRNAs in the cytoplasm forming many densely condensed nucleocapsids (protovirions). Protovirions bind to membrane cSME secreted from the Golgi apparatus to form self-organized virion progeny (Hu et al., 2021; To et al., 2021; V´kovski et al., 2021). Mature progeny virions attach to the cell membrane and are released during exocytosis, their number can reach 10^3 per cell (Bar-On et al., 2020).

The complete productive cycle of a virus consists of the main phases: infection, replication, release, and transmission of virions. Viral gRNA should primarily translate the non-structural polypeptides Pp1a and Pp1ab using cellular ribosomes. Since these polypeptides produce the enzymes necessary for replication and transcription of the genomic and subgenomic RNA of the ßCoV (Yadav et al., 2021; Yoshimoto 2020). The total length of Pp1ab in the SARS-CoV2 virus is 7073 amino acid residues, and the Pp1a polypeptide consists of 4405 amino acid residues (NCBI, 2022; UniProt, 2022). About 85 % of the virus gRNA nucleotides encode Pp1ab and the spike protein.

As an obligatory parasite, the virus uses an intracellular apparatus for the synthesis and post-translational modifications of all the necessary polypeptides, as well as RNA molecules. The remaining components that make up the structure of pathogenic virions are taken from the host cell (Abdelrahman &Wang, 2020; Hu et al., 2021; To et al., 2021; V´kovski et al., 2021).

Type of diet influences the development of COVID-19 disease

Animals need essential macronutrients (proteins, carbohydrates, and lipids) to sustain their life, health, and reproduction. The WHO has long promoted recommendations for healthy eating. Human food must contain the required quantity and quality of basic products and additional nutrients[5] (Wu, 2016; Joint, 2007). The most commonly used staples are rice, wheat, corn, and beans. However, plants are incomplete sources of protein due to their low content of some essential amino acids (EAAs). Vegans are advised to consume additional sources of protein, to achieve the optimal EAAs combination. The diet of many people in some countries or regions is low in calories, uniform, and does not contain the recommended complete protein[6] (Our World in Data, 2022; New Food Balances, 2021).

WHO or the Food and Agriculture Organization (FAO) of the UNO have recommended the optimal amount of dietary protein and the correct ratio of EAAs to maintain quality of life and good health. Protein bioavailability is a criterion for determining the nutritional value of foods (Joint, 2007).

As noted above, diet can significantly influence the development of COVID-19 (Allard at al., 2020; Bedock et al., 2021; Clemente-Suarez et al., 2021; James et al., 2021; Mentella et al., 2021; Mechanick et al., 2021; Morais et al., 2021; Mortaz et al., 2021). In large statistical samples, it has been shown that the severity of COVID-19 was worsened by the consumption of animal proteins in excess of the WHO recommendations (Ponomarenko, 2022; Ponomarenko, 2023). In contrast, a plant-based diet correlated directly with a mild SARS-CoV-2 infection process (Ponomarenko 2022; Kim et al., 2021).

These data were confirmed when comparing the statistical sample for the top 20 countries in terms of the number of infected people (Table S1). The correlation coefficients between animal protein intake and pathogenicity of SARS-CoV-2 varied between 0.83 for infection rate and 0.61 for specific mortality (Table S2). The correlation coefficients between the development of COVID-19 and the consumption of plant foods were lower (-0.30 for RPr and-0.24 for IFR) than in studies conducted before the fifth global wave of the pandemic (Ponomarenko, 2022; Ponomarenko, 2023), which analyzed epidemiological data from a different type of statistical samples. The resulting correlation coefficients (Table S2) confirm that the overconsumption of animal proteins correlates with the severity of COVID-19. It can be assumed that some components of dietary animal proteins were critical factors in the development and outcome of COVID-19 disease.

Comparison of the amino acid composition of proteins from animals, plants, and viruses

Proteins and their AAs are essential for the structure and function of living cells and viruses.

The building blocks of proteins are amino acid residues. Therefore, it is logical to study the dependence of the severity of COVID-19 on the AAs amount and composition of proteins consumed. The significance of viruses' amino acid profile is analyzed here.

Biochemists divide the 20 standard proteinogenic AAs into two groups depending on the ability of the human body to synthesize them: non-essential (NEAAs) and EAAs. The nine EAAs must come from food; the NEAAs are synthesized in various cells of the body.

Edible products differ in the ratio of NEAAs and EAAs. Animal proteins contain more EAAs than plants (Gardner et al., 2019; Gorissen et al., 2018; Kang, 2020). Fish and eggs contain an average of 44 % EAAs, milk, and meat about 43 % (Table 1,

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[5] World Health Organization. https://www.who.int

[6] там же

Table 1

Ratio of total EAAs and LKTV of animal or vegetable based proteins in staple food

	Food						
Amino acid	**Meat**	**Egg-milk**	**Salmon**	**Wheat**	**Rice**	**Potato**	**Soybeans**
Leucine	8,0–8,2	8,5–8,8	8,6	6,7	8,28	6	7,7
Lysine	8,8–9,1	7,2–7,8	9,4	2,2	3,66	6	6,2
Threonine	4,2–4,6	4,0–4,8	4,4	3	3,59	3,6	4,2
Valine	5,2–5,4	6,0	5,2	4,4	6,14	5,5	4,6
Sum LKTV	31,0–33,0	30,5–32,8	32,4	19,8	25,97	25,3	27,3
Total EAAs	41,8–44,3	42,9–43,7	43,8	30,2	37	35	38,5

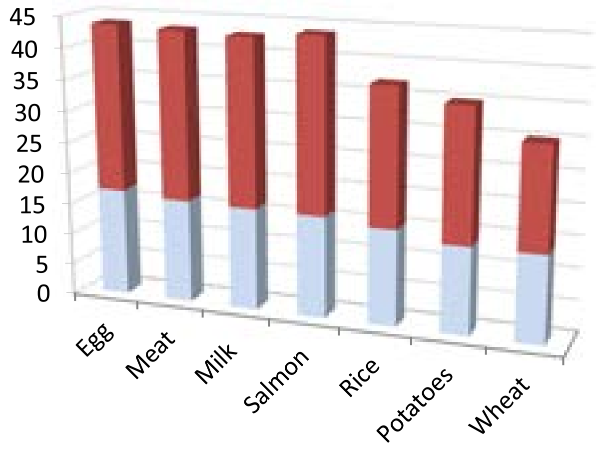
Amount of total EAAs and LKTV in % in meat (from beef, chicken, and pork), egg-milk products, and diet plants (Gardner et al., 2019).

Fig. 1). In the proteins of the main products produced from plants: rice, wheat, potatoes and soybeans; the proportion of EAAs is 37 %, 30 %, 35 %, and 38 %, respectively (Fig. 1, Table 1). An adult should consume 0.8–1 g of protein per kg of body weight (BW) daily (WHO; Joint, 2007) and 0.2 g/kg BW/day EAAs (Verzola et al., 2021). In Europe and America, people consume more total and animal protein (Western diet) (Table 2, Fig. 2) than the WHO recommends[7] (Our World in Data, 2022; New Food Balances, 2021).

More than a half of the EAAs consumed are represented by four amino acids: leucine, lysine, threonine, and valine (LKTV). Their content in food varies greatly depending on the diet. Plant proteins have a low content of EAAs (Fig. 1–3, Tables 1–2) and have a particularly low content of lysine (Gardner et al., 2019; Gorissen et al., 2018; Kang, 2020). Therefore, vegan diets contain less EAAs and LKTV than the diet of meat eaters or the USA standard diet (Paul et al., 2019) (Table 2., Fig. 2). The proteins of the Standard American diet contain almost twice as many LKTV amino acids (Paul et al., 2019; Schmidt et al., 2015; Mariotti & Gardner, 2019) as in the vegan diet (Table 2.). Children generally require more dietary protein per kg of body weight than adults. WHO recommends the amount of total protein and AAs required per day (Table 2, Fig. 2) for optimal body functioning in children and adults[8] (Joint, 2007). However, residents of many countries in Africa and Asia consume much less total protein, and especially less animal protein[9] (Ponomarenko, 2022; Ponomarenko, 2023; Our World in Data, 2022; New Food Balances, 2021).

Fig. 1

Content of total EAAs and LKTV in animal or vegetable dietary proteins



Ratio of total EAAs and LKTV (red), % of total protein, in egg, meat (mean from beef, chicken, and pork), milk products, rice, potato, and wheat (Gardner et al., 2019). On the ordinate axis indicated amount of AAs as percentage of the total protein.

The concentration of amino acids in the blood

AAs from hydrolyzed dietary proteins are absorbed in the intestine and transported into the bloodstream (Bröer & Bröer, 2017; Groen et al., 2015; Horstman et al., 2020; Trommelen et al., 2021). The concentration of each AA in the blood plasma varies widely both under normal conditions (Table 3) and in various pathologies (Verzola et al., 2021; Schmidt et al., 2016; Bröer & Bröer, 2017; Atila et al., 2021; Ansone et al., 2021; Holecek, 2021; Ren et al., 2018). Their concentration in the blood and other tissues may depend on many factors but is successfully regulated in a healthy body (Joint, 2007). The content of free AAs in the bloodstream changes during the day and can significantly increase after a meal (Joint, 2007; Groen et al., 2015; Horstman et al., 2020; Trommelen et al., 2021). Free amino acid (FAA) homeostasis is maintained through the synthe-

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[7] World Health Organization. https://www.who.int

[8] World Health Organization. https://www.who.int

[9] там же

Table 2

Four EAAs content (g) in 100 g of total protein from different diets compared with recommended dietary allowance by WHO

Amino acid	WHO	Human milk	Meat-eaters	Vegans	AD*
Leucine	5,9	9,6	6,13	4,33	7,75
Lysine	4,5	6,9	5,01	2,82	6,69
Threonine	2,3	4,4	2,99	2,19	3,84
Valine	3,9	5,5	4,14	2,95	5,07
Sum LKTV	16,6	26,4	18,27	12,29	23,35
Ref.	(Joint 2007)	(Joint 2007)	(Schmidt et al., 2016)	(Schmidt et al., 2016)	(Paul et al., 2019)

AD* =Standard American Diet,

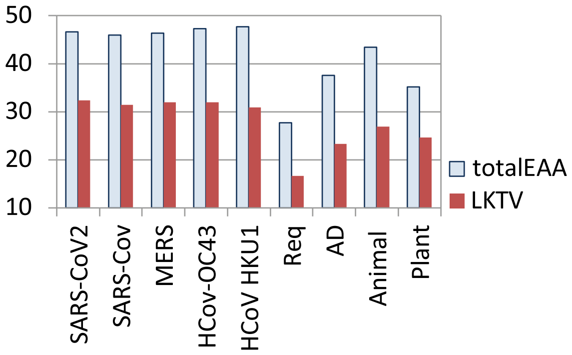
sis/degradation of polypeptides and amino acids, protein proteolysis, AAs uptake from the gut into the bloodstream, and their utilization in various tissues (Joint, 2007; Bröer & Bröer, 2017; Ansone et al., 2021; 2021; Ren et al., 2018; Purpura et al., 2014; Sans et al., 2020). Baseline (fasting) plasma concentrations of some FAAs are lower in vegans (Schmidt et al., 2016; Purpura et al., 2014) than in those who consume animal products (Table 3). The content of EAAs in human muscles is lower than in the proteins of other mammals (Fig. 3). The level of all FAAs and especially EAAs in plasma increases up to 2–3 times after a meal (Paul et al., 2019; Groen et al., 2015; Horstman et al., 2020; Trommelen et al., 2021; Purpura et al., 2014; Wilkinson et al., 2018; Yang et al., 2012), therefore their transport to organs and tissues rises (Groen et al., 2015; Yang et al., 2012). This leads to an intensification in the rate of protein synthesis (Groen et al., 2015; Horstman et al., 2020; Wilkinson et al., 2018; Bohe et al., 2003) and is used by athletes to build muscle mass.

The SARS-CoV-2 virus modifies the consumption profile and distribution of proteins and AAs in host cells and leads to an imbalance in the metabolism of AAs in the body (Mussap & Fanos, 2021; Wu et al., 2021; Verzola et al., 2021; Ansone et al., 2021; Ren et al., 2018). The pathogen alters central cellular pathways such as translation, splicing, carbon metabolism, protein homeostasis (proteostasis), and nucleic acid metabolism (Bojkova et al., 2020; Banerjee et al., 2020). The serum metabolome of COVID-19 patients is distinctive and has important value in investigating pathogenesis, determining a diagnosis, predicting severe cases, and improving treatment (Shi et al., 2021).

The composition of AAs in patients' plasma can vary significantly depending on the severity of COVID-19 (Delattre et al., 2020; Mussap & Fanos, 2021; Paez-Franco et al., 2021; Wu et al., 2021Atila et al., 2021; Ansone et al., 2021; Rees et al., 2021). About 70 % of the three BCAAs: leucine, isoleucine, and valine are transported from the bloodstream to peripheral tissues (Holecek, 2021) and their metabolism is regulated coordinately. BCAAs are essential for the regulation of anabolic process; their transport is interdependent with other AAs (Paez-Franco et al., 2021). Leucine rapidly accelerates protein synthesis (Groen et al., 2015; Wilkinson et al., 2018; Yang et al., 2012; van Sloun et al., 2020).

Fig. 2

Amount of EAAs in proteins from HCoV, animal and plants



Red: LKTV, light blue: total EAAs. AD: standard American Diet (Paul et al., 2019). Animal: mean from meat, milk and egg products (Gardner et al., 2019). Plant: mean from rice, wheat, potato, and soya (Gardner et al., 2019). Req: amount of EAAs required per day (WHO; Joint 2007). For HCoV protein sequences used means of Pp1ab+Spike which UniProtKB-ID listed in Table S2 (uniprot). On the ordinate axis indicated amount of EAAs as percentage of the total protein.

The peculiarity of AAs composition of virus polypeptides

Virus polypeptides are very different from human proteins, other animals, or plants in terms of the amount of EAAs and their proportion in the total protein. The proportion of EAAs in HCoV proteins is much higher than in mammalian tissues (Fig. 1–3). The proteins of the HCoV-HKU1 Coronavirus contain the highest amount of EAAs, and the SARS-CoV2 virus contains more of the LKTV compared to other HCoVs (Fig. 2–3). Nutrient plant proteins contain much less of both

Table 3

Content of selected EAAs in blood plasma, human tissues and diet proteins

Amino acid	Plasma AAs [μmol/L]			% of total protein			
	Reference intervals	Meat-eaters	Vegan	Human body	Human muscle	Meat	Plant
Leucine	66–170	205	191	7,5	7,6	8,1	7,2
Lysine	150–220	241	210	7,3	7,8	9,0	4,5
Threonine	92–240	164	165	4,2	3,4	4,4	3,6
Valine	150–310	230	217	4,9	5,1	5,3	5,2
Ref.	*	(Schmidt et al., 2016)		(Joint, 2007)	(Gorissen et al., 2018; 0 et al., 2019)		

Meat and Plant: average composition (%) of EAAs in ingested 100 g dietary meat and plant products (from Table 1).

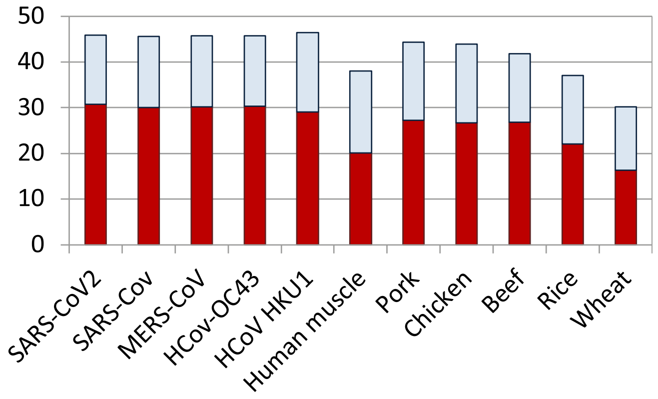
*https://www.ucsfhealth.org/

EAAs and LKTV than Coronaviruses or human and animal proteins (Table 1, Fig. 2–3).

The spike protein and other structural polypeptides of Coronaviruses have a high content of leucine, threonine, and valine (Renz et al., 2021). Polyproteins of Coronaviruses are synthesized just after entry into the cell (V´kovski et al., 2021;Yadav et al., 2021) and have an EAAs content of more than 45 % (Fig. 4). The Pp1a polyprotein of the HCoV-HKU1 virus is almost half composed of EAAs residues. Another feature of the proteins of HCoV viruses is the high content of four LKTV amino acid residues, almost 1/3 of all AAs (Fig. 2–3). SARS-CoV-2 Coronavirus proteins contain more valine and threonine than alveolar cells (Renz et al., 2020) and diet proteins (Fig. 5). The content of EAAs is highest in the Pp1a polyprotein (Fig. 4).

Fig. 3

Amount of EAAs in proteins from human beta-coronaviruses, animal and plants



Red: LKTV, light blue: the rest EAAs of total protein. For HCoV proteins used means of Pp1ab+Spike which UniProtKB-ID listed in Table S2 (uniprot). Human muscle: ratio EAAs, % of total protein in human muscle, in animal and plant food (Gorissen et al., 2018). On the ordinate axis indicated amount of AAs as percentage of the total protein.

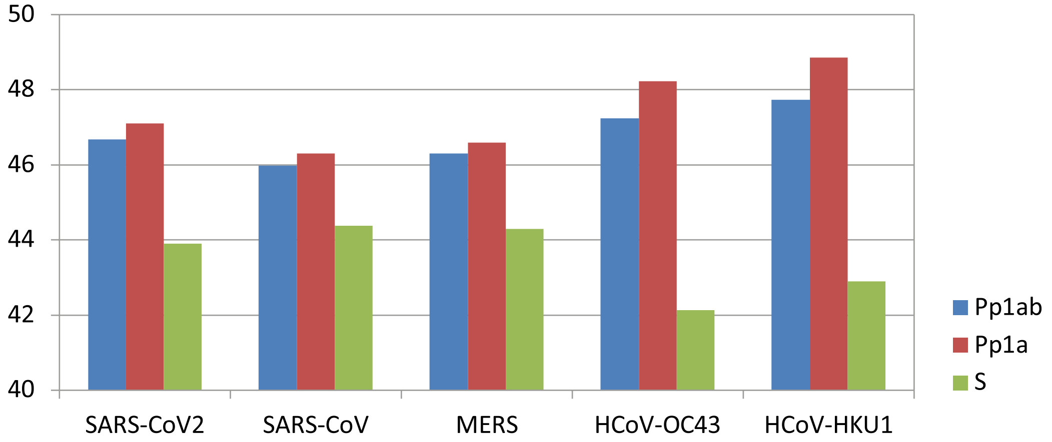
Vegans consume only half as much lysine as meat eaters. The SARS-CoV-2 polyprotein Pp1a contains 2–3 times more threonine or valine than consumed proteins (Fig. 5). The Pp1a proteins of HCoV-OC43 and HCoV-HKU1 contain twice as much valine as mammalian tissues. The highest content of threonine is in Pp1a of the SARS-CoV-2 virus. A significant amount of leucine (more than 9 %) is found in all five pathogenic HCoV viruses. It is not clear; can leucine increase protein synthesis of the virus as has been noted for cell proteins translation (Groen et al., 2015; Sans et al., 2021; Cantwell et al., 2021). The SARS-CoV-2 virus causes metabolic reprogramming of the AAs profile, and competition between host and pathogen for EAAs is not excluded (Paez-Franco et al., 2021; Wu et al., 2021; Rees et al., 2021; Lapointe et al., 2021). AAs deficiency can reduce translation (Sans et al., 2021), and leucine deficiency inhibits the formation of intracellular polysomes (Mazor et al., 2018).

SARS-CoV-2 reproduction and translation kinetics

The kinetics of reproduction of viruses, as well as other microorganisms, obeys the Monod equation, which is similar to the dependence of Michaelis-Menten on the concentration of the substrate for the enzymatic reaction (Cheemarla et al., 2021; Pyke et al., 2021). These equations describe the reaction rate as a function of substrate concentration. At a concentration of translation substrates sufficient for the optimal rate of pathogen protein synthesis, virion replication passes through the lag phase and the fast phase into the exponential growth phase (Cheemarla et al., 2021; Pyke et al., 2021). The doubling time of the SARS-CoV-2 virus is 6–10 hours (Cheemarla et al., 2021; Bar-On et al., 2020). Each pneumocyte type2 (PT2) can produce about a thousand new virions (Bar-On et al., 2020). At the peak of pathogenesis in the

Fig. 4

Ratio of total EAAs in five HCoVs proteins



Total amount of EAAs in proteins (%) of Pp1a, Pp1ab and Spike protein of HCoVs, which UniProtKB-ID listed in Table S2 (uniprot). On the ordinate axis indicated amount of AAs as percentage of the total protein.

body of an infected patient, the total number of viral particles reaches 10^9–10^{11} with a mass greater than 100 g (Bar-On et al., 2020). As a result of the successful reproduction of the SARS-CoV-2 virus, lung weight increases, but the total body weight of animals (Cantwell et al., 2021) or humans (Bedock et al., 2021) decreases.

The expression rate of viral polypeptides rapidly increases after the lag phase (Aller et al., 2018; Cheemarla et al., 2021; Pyke et al., 2021). The polypeptides of the SARS-CoV-2 virus are elongated by 6 AA residues per second (Bar-On et al., 2020). Some NSPs mediate cellular RNAs destabilization but stimulate robust translation of viral gRNAs and subgenomic RNAs (Lapointe et al., 2021; Zhang et al., 2022). More than 60 mutations were found in Omicron variant B.1.1.529 (GSAI ID: R40B60_BHP_3321001247/2021) of the SARS-CoV-2 virus, as a result of which the content of EAAs changed. This led to an alteration in the development dynamics of this pathogen (He et al., 2021). For the log phase of protein synthesis, it is necessary that the concentration of free and transportable AAs significantly exceed Km (Bergström et al., 1974; Hoffmann & Lambert, 1983).

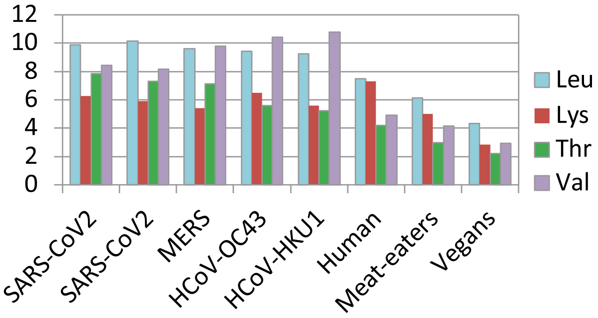
The large difference between the need and availability of LKTV makes them the first limiting substrates in the polymerization reaction of HCoV polypeptides. A reasonably high concentration of LAAs is required to enter the exponential phase of the synthetic reaction. A lack of even one AA can slow down or interrupt the translation of Coronavirus polyproteins (Verzola et al., 2021) and, therefore, a low concentration of LAAs can block the synthesis of NSPs.

Factors affecting the rate of translation of SARS-CoV-2 polypeptides

The HCoV-HKU1 virus contains more EAAs than the three SARS-causing pathogens and has more than 10 % valine in its Pp1ab polypeptide (Fig. 2–3, 5). The deficiency of EAAs will interrupt the Pp1a translation, which is known as the first synthesized in HCoV. Inhibition of translation of functional Pp1a and Pp1ab polypeptides can consequently lead to a radical decrease in the rate of synthesis of Coronavirus gRNA and subgenomic RNAs and the polypeptides they encode. Such a decrease in the synthesis rate of Pp1a molecules or abortive translation can prevent the development of the log phase of replication, reduce the pathogenic effect of the virus, and prevent cytokine storms in COVID-19 patients.

Fig. 5

Content of selected EAAs in HCoV, in human and in food as percentage of total protein



Human: % of EAAs in whole body (Joint, 2007). Meat-eaters and Vegans: composition (%) of EAA in ingested 100 g food proteins by meat-eaters or vegans (Schmidt et al., 2016). For HCoVs used sequence of polyprotein Pp1a which UniProtKB-ID listed in Table S2 (uniprot). On the ordinate axis indicated amount of AAs as percentage of the total protein.

The high concentration of EAAs in the polyproteins Pp1a or Pp1ab, especially valine, may explain the less severe outcomes of the two human coronaviruses HCoV-OC43 and HCoV-HKU1 infection compared to COVID-19.

Table 4 structures the data, showing that optimal conditions in PT2 for the protein synthesis of the SARS-CoV-2 virus were created. In the alveoli cells were observed a high level of protein expression. The interaction of the synthesizing systems of the cell and the virus can provide high-speed translation on host ribosomes (Zhang et al., 2022). A high rate of viral protein synthesis is necessary for a short replication cycle and efficient production of a large population of progeny virions. The amount of LKTV may be the primary limiting factor in the rate of polypeptide translation, and hence the replication of the SARS-CoV-2 virus. The high requirement of Pp1a and proteins for EAAs makes their replication very sensitive, especially to the shortage of LKTV. Such lack of LAAs can lead to inhibition of SARS-CoV-2 virus replication or even unproductive infection.

Table 4

Conditions for fast replication of SARS-CoV-2 virus in pneumocytes

Drivers of translation and replication	Factors promoting viral protein synthesis
Intracellular structures and mechanisms provide a high rate of viral protein synthesis.	The ability of PT2 to form transcriptional-translational complexes inside membrane vesicles supplies a high rate of synthesis of gRNA and subgenomic RNAs of the SARS-CoV-2 virus (Bar-On et al., 2020; Fehrenbach, 2001; Knudsen & Ochs, 2018). The ability of PT2 to a high rate of protein synthesis provides a highly developed rER and amino acid transport ATPases (Fehrenbach, 2001; Knudsen & Ochs, 2018; Mason, 2006; Weibel, 2015). A large number of mitochondria and a saturated oxygen concentration in PT2 create good conditions for enhanced oxidative phosphorylation and ensure high production of nucleoside triphosphates (NTP) and other energy-rich molecules required for the high-speed synthesis of RNA and polypeptides, and virus titer (Bedock et al., 2020; Lapointe et al., 2021; Zhang et al., 2022).
SARS-CoV-2 virus alters and suppresses host protein synthesis	Viral proteins inhibit the synthesis of host cell polypeptides, and induce changes the properties of the synthesized host proteins. This leads to an alteration in the cell cycle and RNA splicing (Finkel et al., 2021; Banerjee et al., 2020; Lapointe et al., 2021).
Timely sufficient concentrations of necessary FAAs in cells. Prolonged high concentration of EAAs in plasma and their active transport into the cell.	Deficiency of AAs in contrast to their excess amount causes inhibition of intracellular translation and decreases in protein synthesis (Bröer & Bröer, 2017). In the cytosol of cells, the concentration of AAs is higher than in plasma (Bröer & Bröer, 2017; Holecek, 2021; Bergström et al., 1974; Hoffmann & Lambert, 1983). The content of threonine and valine in lung cells is lower than in SARS-CoV-2 proteins (Renz et al., 2020).
Metabolic mechanisms capable of accelerating translation on the ribosomes of the cell	It is known that leucine induces intracellular translation (Sans et al., 2021; Mazor et al., 2018). A high concentration of FAAs in plasma activates the activity of anabolic hormones. Animal proteins are more anabolic than ones of plant origin (Verzola et al., 2021].
The intake of AAs from the intestine and from the breakdown products of host own proteins. Anabolic hormones inhibit the breakdown of proteins in the body; therefore, in the postprandial period, the role of ingested proteins for the transport of AAs to the tissue increases.	AAs are accumulated in plasma and most of FAAs are transported to tissues (Groen et al., 2015; Trommelen et al., 2021). The postprandial plasma concentration of AAs, including leucine, is increased for 2–5 hours (Groen et al., 2015; Horstman et al., 2020), depending on the composition of the food. After a peak, they decrease back to base levels (Schmidt et al., 2016;Bröer & Bröer, 2017). Anabolic hormones not only stimulate protein synthesis, but they also inhibit protein breakdown as well (Bohe et al., 2003; van Sloun et al., 2020).
Consumption of a large amount of highly bioavailable foods with a high content of proteinogenic AAs.	In the process of enzymatic digestion, a pool of FAAs is formed in the bloodstream, and the concentration of EEAs increases significantly with a sufficient level of nutrition. A high concentration of FAAs is required for the accelerated synthesis of viral proteins (Ren et al., 2018).
The basic concentration of FAAs is regulated by complex systems, both at the level of the cell and total organism	The bioavailability of AAs from animal proteins is higher than that from plant proteins. Consumption of large amounts of animal proteins provides a high content of EAAs, which leads to a high rate of polypeptide synthesis in animal tissues. Plant-based food contains a minor amount of EAAs and gives a less postprandial increase of FAAs (Schmidt et al., 2016; Purpura et al., 2014).

CONCLUSIONS

SARS-CoV-2 coronavirus causes COVID-19 disease in humans. The pandemic of this infectious disease has been depressing the vital activity of mankind for more than three years. Effective methods were urgently needed to combat COVID-19.

So far, no reliable data have been obtained on the effective use of an etiological drug that suppresses the early translation of the proteins of this pathogenic virus.

The relationship between diet type and the impact of the COVID-19 pandemic in the top 20 countries by the number of infections has been explored using numerous available statistics. A positive correlation between the severity of COVID-19 outcome and protein intake has been identified previously for many regions and confirmed by this analysis.

The SARS-CoV-2 virus interacts with human ACE2 receptors, multiplies rapidly in affected cells, and critically alters proteostasis and AAs homeostasis in the host organism.

Coronaviruses, after invasion into the cell, must translate the polyproteins Pp1a and Pp1ab. These polypeptides of Coronaviruses, unlike the proteins of the human body, other animals, and plants, contain a very high amount of EAAs. The proportion of EAAs is the highest in the Pp1a polyprotein, namely 47 % of the total protein in the SARS-CoV-2 virus. Almost one-third of the total amino acid composition of Pp1a is represented by four EAAs: leucine; lysine; threonine and valine. The limited availability of one of these substrates can lead to a disruption in the polymerization rate of the Pp1a and Pp1ab polypeptide chains and, subsequently, to inhibition of SARS-CoV-2 early stage of replication.

EAAs are not synthesized *de novo* in the human body. Most of EAAs enter all tissues of the body from food. With a low-calorie diet, and a predominantly plant-based diet, a small amount of EAAs enters the bloodstream. It should be noted that protein intake below the WHO recommendation does not protect against the spread or invasion of viral particles. In regions where diets are predominantly low in these LAAs, infected patients may have asymptomatic or mild COVID-19 disease, without the post-COVID syndrome.

This study has analyzed the relationship between COVID-19 outcomes and the amount of animal protein consumption. Comparison of the AAs composition of the SARS-CoV-2 pathogen and the host let to propose that the limit of LKTV can be a critical factor for the rapid synthesis of Pp1a and Pp1ab polyproteins. More detailed biochemical investigations need after that understanding of the EEAs responsibility in the relationship between virus and host.

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REFERENCES

Abdelrahman, Z., Li, M., & Wang, X. (2020). Comparative Review of SARS-CoV-2, SARS-CoV, MERS-CoV, and Influenza A Respiratory Viruses. *Frontiers in Immunology*, *11*, 552909. https://doi.org/10.3389/fimmu.2020.552909

Allard, L., Ouedraogo, E., Molleville, J., Bihan, H., Giroux-Leprieur, B., Sutton, A., Baudry, C., Josse, C., Didier, M., Deutsch, D., Bouchaud, O., & Cosson, E. (2020). Malnutrition: Percentage and Association with Prognosis in Patients Hospitalized for Coronavirus Disease 2019. *Nutrients, 12*(12), 3679. https://doi.org/10.3390/nu12123679

Aller, S., Scott, A., Sarkar-Tyson, M., & Soyer, O. S. (2018). Integrated human-virus metabolic stoichiometric modelling predicts host-based antiviral targets against Chikungunya, Dengue and Zika viruses. *Journal of the Royal Society, Interface*, *15*(146), 20180125. https://doi.org/10.1098/rsif.2018.0125

Atila, A., Alay, H., Yaman, M. E., Akman, T. C., Cadirci, E., Bayrak, B., Celik, S., Atila, N. E., Yaganoglu, A. M., Kadioglu, Y., Halıcı, Z., Parlak, E., & Bayraktutan, Z. (2021). The serum amino acid profile in COVID-19. *Amino Acids*, *53*(10), 1569–1588. https://doi.org/10.1007/s00726–021-03081-w

Banerjee, A. K., Blanco, M. R., Bruce, E. A., Honson, D. D., Chen, L. M., Chow, A., Bhat, P., Ollikainen, N., Quinodoz, S. A., Loney, C., Thai, J., Miller, Z. D., Lin, A. E., Schmidt, M. M., Stewart, D. G., Goldfarb, D., De Lorenzo, G., Rihn, S. J., Voorhees, R. M., Botten, J. W., … Guttman, M. (2020). SARS-CoV-2 Disrupts Splicing, Translation, and Protein Trafficking to Suppress Host Defenses. *Cell*, *183*(5), 1325–1339.e21. https://doi.org/10.1016/j.cell.2020.10.004

Bar-On, Y. M., Flamholz, A., Phillips, R., & Milo, R. (2020). SARS-CoV-2 (COVID-19) by the numbers. *eLife*, 9, e57309. https://doi.org/10.7554/eLife.57309

Bedock, D., Couffignal, J., Bel Lassen, P., Soares, L., Mathian, A., Fadlallah, J. P., Amoura, Z., Oppert, J. M., & Faucher, P. (2021). Evolution of Nutritional Status after Early Nutritional Management in COVID-19 Hospitalized Patients. *Nutrients, 13*(7), 2276. https://doi.org/10.3390/nu13072276

Bergström, J., Fürst, P., Norée, L. O., & Vinnars, E. (1974). Intracellular free amino acid concentration in human muscle tissue. *Journal of Applied Physiology*, *36*(6), 693–697. https://doi.org/10.1152/jappl.1974.36.6.693

Bhatt, P. R., Scaiola, A., Loughran, G., Leibundgut, M., Kratzel, A., Meurs, R., Dreos, R., O'Connor, K. M., McMillan, A., Bode, J. W., Thiel, V., Gatfield, D., Atkins, J. F., & Ban, N. (2021). Structural basis of ribosomal frameshifting during translation of the SARS-CoV-2 RNA genome. *Science (New York, N.Y.)*, *372*(6548), 1306–1313. https://doi.org/10.1126/science.abf3546

Billinger, E., Zuo, S., & Johansson, G. (2019). Characterization of Serine Protease Inhibitor from *Solanum tuberosum* Conjugated to Soluble Dextran and Particle Carriers. *ACS Omega*, *4*(19), 18456–18464. https://doi.org/10.1021/acsomega.9b02815

Bohé, J., Low, A., Wolfe, R. R., & Rennie, M. J. (2003). Human muscle protein synthesis is modulated by extracellular, not intramuscular amino acid availability: a dose-response study. *The Journal of Physiology*, *552*(Pt 1), 315–324. https://doi.org/10.1113/jphysiol.2003.050674

Bojkova, D., Klann, K., Koch, B., Widera, M., Krause, D., Ciesek, S., Cinatl, J., & Münch, C. (2020). Proteomics of SARS-CoV-2-infected host cells reveals therapy targets. *Nature*, *583*(7816), 469–472. https://doi.org/10.1038/s41586–020-2332–7

Bröer, S., & Bröer, A. (2017). Amino acid homeostasis and signalling in mammalian cells and organisms. *The Biochemical Journal*, *474*(12), 1935–1963. https://doi.org/10.1042/BCJ20160822

Cantwell, A. M., Singh, H., Platt, M., Yu, Y., Lin, Y. H., Ikeno, Y., Hubbard, G., Xiang, Y., Gonzalez-Juarbe, N., & Dube, P. H. (2021). Kinetic Multi-omic Analysis of Responses to SARS-CoV-2 Infection in a Model of Severe COVID-19. *Journal of Virology*, *95*(20), e0101021. https://doi.org/10.1128/JVI.01010–21

CDC. Centers for Disease Control and Prevention. (2022). COVID-19.Cases & data [Data set]. https://www.cdc.gov/coronavirus/2019-ncov/

Cheemarla, N. R., Watkins, T. A., Mihaylova, V. T., Wang, B., Zhao, D., Wang, G., Landry, M. L., & Foxman, E. F. (2021). Dynamic innate immune response determines susceptibility to SARS-CoV-2 infection and early replication kinetics. *The Journal of Experimental Medicine*, *218*(8), e20210583. https://doi.org/10.1084/jem.20210583

Clemente-Suárez, V. J., Ramos-Campo, D. J., Mielgo-Ayuso, J., Dalamitros, A. A., Nikolaidis, P. A., Hormeño-Holgado, A., & Tornero-Aguilera, J. F. (2021). Nutrition in the Actual COVID-19 Pandemic. A Narrative Review. *Nutrients*, *13*(6), 1924. https://doi.org/10.3390/nu13061924

Delattre, H., Sasidharan, K., & Soyer, O. S. (2020). Inhibiting the reproduction of SARS-CoV-2 through perturbations in human lung cell metabolic network. *Life Science Alliance*, *4*(1), e202000869. https://doi.org/10.26508/lsa.202000869

Fehrenbach, H. (2001). Alveolar epithelial type II cell: defender of the alveolus revisited. *Respiratory Research,* 2, 33. https://doi.org/10.1186/rr36

Finkel, Y., Gluck, A., Nachshon, A., Winkler, R., Fisher, T., Rozman, B., Mizrahi, O., Lubelsky, Y., Zuckerman, B., Slobodin, B., Yahalom-Ronen, Y., Tamir, H., Ulitsky, I., Israely, T., Paran, N., Schwartz, M., & Stern-Ginossar, N. (2021). SARS-CoV-2 uses a multipronged strategy to impede host protein synthesis. *Nature*, *594*(7862), 240–245. https://doi.org/10.1038/s41586–021-03610–3

Gardner, C. D., Hartle, J. C., Garrett, R. D., Offringa, L. C., & Wasserman, A. S. (2019). Maximizing the intersection of human health and the health of the environment with regard to the amount and type of protein produced and consumed in the United States. *Nutrition Reviews*, *77*(4), 197–215. https://doi.org/10.1093/nutrit/nuy073

Gorissen, S. H. M., Crombag, J. J. R., Senden, J. M. G., Waterval, W. A. H., Bierau, J., Verdijk, L. B., & van Loon, L. J. C. (2018). Protein content and amino acid composition of commercially available plant-based protein isolates. *Amino acids*, *50*(12), 1685–1695. https://doi.org/10.1007/s00726–018-2640–5

Groen, B. B., Horstman, A. M., Hamer, H. M., de Haan, M., van Kranenburg, J., Bierau, J., Poeze, M., Wodzig, W. K., Rasmussen, B. B., & van Loon, L. J. (2015). Post-Prandial Protein Handling: You Are What You Just Ate. *PloS one*, *10*(11), e0141582. https://doi.org/10.1371/journal.pone.0141582

He, X., Hong, W., Pan, X., Lu, G., & Wei, X. (2021). SARS-CoV-2 Omicron variant: Characteristics and prevention. *MedComm*, *2*(4), 838–845. https://doi.org/10.1002/mco2.110

Hoffmann, E. K., & Lambert, I. H. (1983). Amino acid transport and cell volume regulation in Ehrlich ascites tumour cells. *The Journal of Physiology*, *338*, 613–625. https://doi.org/10.1113/jphysiol.1983.sp014692

Holeček M. (2021). The role of skeletal muscle in the pathogenesis of altered concentrations of branched-chain amino acids (valine, leucine, and isoleucine) in liver cirrhosis, diabetes, and other diseases. *Physiological Research*, *70*(3), 293–305. https://doi.org/10.33549/physiolres.934648

Horstman, A. M. H., Ganzevles, R. A., Kudla, U., Kardinaal, A. F. M.. van den Borne, J. J. G. C., & Huppertz, T. (2021). Postprandial blood amino acid concentrations in older adults after consumption of dairy products: The role of the dairy matrix. *International Dairy Journal*, *113*. https://doi.org/10.1016/j.idairyj.2020.104890

Hu, B., Guo, H., Zhou, P., & Shi, Z. L. (2021). Characteristics of SARS-CoV-2 and COVID-19. *Nature reviews. Microbi-*

ology, *19*(3), 141–154. https://doi.org/10.1038/s41579–020-00459–7

James, P. T., Ali, Z., Armitage, A. E., Bonell, A., Cerami, C., Drakesmith, H., Jobe, M., Jones, K. S., Liew, Z., Moore, S. E., Morales-Berstein, F., Nabwera, H. M., Nadjm, B., Pasricha, S. R., Scheelbeek, P., Silver, M. J., Teh, M. R., & Prentice, A. M. (2021). The Role of Nutrition in COVID-19 Susceptibility and Severity of Disease: A Systematic Review. *The Journal of Nutrition*, *151*(7), 1854–1878. https://doi.org/10.1093/jn/nxab059

Joint WHO/FAO/UNU Expert Consultation (2007). Protein and amino acid requirements in human nutrition. *World Health Organization technical report series*, (935).

Kang J. S. (2020). Dietary restriction of amino acids for Cancer therapy. *Nutrition & Metabolism*, *17*, 20. https://doi.org/10.1186/s12986–020-00439-x

Kim, H., Rebholz, C. M., Hegde, S., LaFiura, C., Raghavan, M., Lloyd, J. F., Cheng, S., & Seidelmann, S. B. (2021). Plant-based diets, pescatarian diets and COVID-19 severity: a population-based case-control study in six countries. *BMJ Nutrition, Prevention & Health.* https://doi.org/10.1136/bmjnph-2021–000272

Komarnytsky, S., Cook, A., & Raskin, I. (2011). Potato protease inhibitors inhibit food intake and increase circulating cholecystokinin levels by a trypsin-dependent mechanism. *International Journal of Obesity (2005)*, *35*(2), 236–243. https://doi.org/10.1038/ijo.2010.192

Knudsen, L., & Ochs, M. (2018). The micromechanics of lung alveoli: structure and function of surfactant and tissue components. *Histochemistry and cell biology*, *150*(6), 661–676. https://doi.org/10.1007/s00418–018-1747–9

Lapointe, C. P., Grosely, R., Johnson, A. G., Wang, J., Fernández, I. S., & Puglisi, J. D. (2021). Dynamic competition between SARS-CoV-2 NSP1 and mRNA on the human ribosome inhibits translation initiation. *Proceedings of the National Academy of Sciences of the United States of America*, *118*(6), e2017715118. https://doi.org/10.1073/pnas.2017715118

Mason, R. J. (2006). Biology of alveolar type II cells. *Respirology,* (11), S12–S15 https://onlinelibrary.wiley.com/doi/pdf/10.1111/j.1440–1843.2006.00800.x

Mariotti, F., & Gardner, C. D. (2019). Dietary Protein and Amino Acids in Vegetarian Diets-A Review. *Nutrients*, *11*(11), 2661. https://doi.org/10.3390/nu11112661

Mazor, K. M., Dong, L., Mao, Y., Swanda, R. V., Qian, S. B., & Stipanuk, M. H. (2018). Effects of single amino acid deficiency on mRNA translation are markedly different for methionine versus leucine. *Scientific Reports*, *8*(1), 8076. https://doi.org/10.1038/s41598–018-26254–2

Mechanick, J. I., Carbone, S., Dickerson, R. N., Hernandez, B. J. D., Hurt, R. T., Irving, S. Y., Li, D. Y., McCarthy, M. S., Mogensen, K. M., Gautier, J. B. O., Patel, J. J., Prewitt, T. E., Rosenthal, M., Warren, M., Winkler, M. F., McKeever, L., & ASPEN COVID-19 Task Force on Nutrition Research (2021). Clinical Nutrition Research and the COVID-19 Pandemic: A Scoping Review of the ASPEN COVID-19 Task Force on Nutrition Research. *JPEN. Journal of Parenteral and Enteral Nutrition*, *45*(1), 13–31. https://doi.org/10.1002/jpen.2036

Mei, M., & Tan, X. (2021). Current Strategies of Antiviral Drug Discovery for COVID-19. *Frontiers in Molecular Biosciences*, *8*, 671263. https://doi.org/10.3389/fmolb.2021.671263

Mentella, M. C., Scaldaferri, F., Gasbarrini, A., & Miggiano, G. A. D. (2021). The role of nutrition in the COVID-19 pandemic. *Nutrients*, *13*(4), 1093. https://doi.org/10.3390/nu13041093

Morais, A. H. A., Aquino, J. S., da Silva-Maia, J. K., Vale, S. H. L., Maciel, B. L. L., & Passos, T. S. (2021). Nutritional status, diet and viral respiratory infections: perspectives for severe acute respiratory syndrome coronavirus 2. *The British Journal of Nutrition*, *125*(8), 851–862. https://doi.org/10.1017/S0007114520003311

Mortaz, E., Bezemer, G., Alipoor, S. D., Varahram, M., Mumby, S., Folkerts, G., Garssen, J., & Adcock, I. M. (2021). Nutritional impact and its potential consequences on COVID-19 severity. *Frontiers in Nutrition*, *8*, 698617. https://doi.org/10.3389/fnut.2021.698617

Mussap, M., & Fanos, V. (2021). Could metabolomics drive the fate of COVID-19 pandemic? A narrative review on lights and shadows. *Clinical Chemistry and Laboratory Medicine*, *59*(12), 1891–1905. https://doi.org/10.1515/cclm-2021–0414

NCBI. (2022). National Center for Biotechnology Information [Data set] https://www.ncbi.nlm.nih.gov/

New Food Balances. (2021). FAOSTAT. Food and agriculture data [Data set]. https://www.fao.org/faostat/en/#home

Our World in Data. (2022). Research and data to make progress against the world's largest problems [Data set]. https://ourworldindata.org

Páez-Franco, J. C., Torres-Ruiz, J., Sosa-Hernández, V. A., Cervantes-Díaz, R., Romero-Ramírez, S., Pérez-Fragoso, A., Meza-Sánchez, D. E., Germán-Acacio, J. M., Maravillas-Montero, J. L., Mejía-Domínguez, N. R., Ponce-de-León, A., Ulloa-Aguirre, A., Gómez-Martín, D., & Llorente, L. (2021). Metabolomics analysis reveals a modified amino acid metabolism that correlates with altered oxygen homeostasis in COVID-19 patients. *Scientific Reports*, *11*(1), 6350. https://doi.org/10.1038/s41598–021-85788–0

Paul, C., Leser, S., & Oesser, S. (2019). Significant amounts of functional collagen peptides can be incorporated in the diet while maintaining indispensable amino acid balance. *Nutrients*, *11*(5), 1079. https://doi.org/10.3390/nu11051079

Ponomarenko, S. V. (2022). Dietary factors influencing the COVID-19 epidemic process. *Farmakoekonomika. Mod-*

ern Pharmacoeconomics and Pharmacoepidemiology, 15(4), 463–471. https://doi.org/10.17749/2070–4909/farmakoekonomika.2022.135

Ponomarenko, S. V. (2023). Statistical analysis of critical socioeconomic factors in the development of COVID-19 disease. *Voprosy statistiki*, *30*(1), 90–100. https://doi.org/10.34023/2313–6383-2023–30-1–90-100

Purpura M., Lowery R. P., Joy J. M., De Souza, E. O., Kalman, D. S., Jäger, R. & Wilson, J. M. (2014). A comparison of blood amino acid concentrations following ingestion of rice and whey protein isolate: A double-blind crossover study. *Journal of Nutrition and Health Sciences, 1*(3), 306.

Pyke, A. T., Nair, N., van den Hurk, A. F., Burtonclay, P., Nguyen, S., Barcelon, J., Kistler, C., Schlebusch, S., McMahon, J., & Moore, F. (2021). Replication kinetics of B.1.351 and B.1.1.7 SARS-CoV-2 variants of concern including assessment of a B.1.1.7 mutant carrying a defective ORF7a gene. *Viruses*, *13*(6), 1087. https://doi.org/10.3390/v13061087

Rees, C. A., Rostad, C. A., Mantus, G., Anderson, E. J., Chahroudi, A., Jaggi, P., Wrammert, J., Ochoa, J. B., Ochoa, A., Basu, R. K., Heilman, S., Harris, F., Lapp, S. A., Hussaini, L., Vos, M. B., Brown, L. A., & Morris, C. R. (2021). Altered amino acid profile in patients with SARS-CoV-2 infection. *Proceedings of the National Academy of Sciences of the United States of America*, *118*(25), e2101708118. https://doi.org/10.1073/pnas.2101708118

Ren, W., Rajendran, R., Zhao, Y., Tan, B., Wu, G., Bazer, F. W., Zhu, G., Peng, Y., Huang, X., Deng, J., & Yin, Y. (2018). Amino acids as mediators of metabolic cross talk between host and pathogen. *Frontiers in Immunology*, *9*, 319. https://doi.org/10.3389/fimmu.2018.00319

Renz, A., Widerspick, L., & Dräger, A. (2020). FBA reveals guanylate kinase as a potential target for antiviral therapies against SARS-CoV-2. *Bioinformatics (Oxford, England)*, *36*(Suppl 2), i813–i821. https://doi.org/10.1093/bioinformatics/btaa813

Renz, A., Widerspick, L., & Dräger, A. (2021). Genome-scale metabolic model of infection with SARS-CoV-2 mutants confirms guanylate kinase as robust potential antiviral target. *Genes*, *12*(6), 796. https://doi.org/10.3390/genes12060796

Sans, M. D., Crozier, S. J., Vogel, N. L., D'Alecy, L. G., & Williams, J. A. (2021). Dietary protein and amino acid deficiency inhibit pancreatic digestive enzyme mRNA translation by multiple mechanisms. *Cellular and Molecular Gastroenterology And Hepatology*, *11*(1), 99–115. https://doi.org/10.1016/j.jcmgh.2020.07.008

Schmidt, J. A., Rinaldi, S., Scalbert, A., Ferrari, P., Achaintre, D., Gunter, M. J., Appleby, P. N., Key, T. J., & Travis, R. C. (2016). Plasma concentrations and intakes of amino acids in male meat-eaters, fish-eaters, vegetarians and vegans: a cross-sectional analysis in the EPIC-Oxford cohort. *European Journal of Clinical Nutrition*, *70*(3), 306–312. https://doi.org/10.1038/ejcn.2015.144

Shi, D., Yan, R., Lv, L., Jiang, H., Lu, Y., Sheng, J., Xie, J., Wu, W., Xia, J., Xu, K., Gu, S., Chen, Y., Huang, C., Guo, J., Du, Y., & Li, L. (2021). The serum metabolome of COVID-19 patients is distinctive and predictive. *Metabolism: Clinical and Experimental*, *118*, 154739. https://doi.org/10.1016/j.metabol.2021.154739

Sloun, B. V., Goossens, G. H., Erdos, B., Lenz, M., Riel, N. V., & Arts, I. C. W. (2020). The impact of amino acids on postprandial glucose and insulin kinetics in humans: A quantitative overview. *Nutrients*, *12*(10), 3211. https://doi.org/10.3390/nu12103211

Srikanth, S., & Chen, Z. (2016). Plant protease inhibitors in therapeutics-focus on cancer therapy. *Frontiers in pharmacology*, *7*, 470. https://doi.org/10.3389/fphar.2016.00470

To, K. K., Sridhar, S., Chiu, K. H., Hung, D. L., Li, X., Hung, I. F., Tam, A. R., Chung, T. W., Chan, J. F., Zhang, A. J., Cheng, V. C., & Yuen, K. Y. (2021). Lessons learned 1 year after SARS-CoV-2 emergence leading to COVID-19 pandemic. *Emerging Microbes & Infections*, *10*(1), 507–535. https://doi.org/10.1080/22221751.2021.1898291

Trommelen J., Tome D., & van Loon L. C. (2021). Gut amino acid absorption in humans: Concepts and relevance for postprandial metabolism. *Clinical Nutrition Open Science, 36*, 43e55 https://doi.org/10.1016/j.nutos.2020.12.006

Uchiyama, T., Fujita, T., Gukasyan, H. J., Kim, K. J., Borok, Z., Crandall, E. D., & Lee, V. H. (2008). Functional characterization and cloning of amino acid transporter B(0,+) (ATB(0,+)) in primary cultured rat pneumocytes. *Journal of cellular physiology*, *214*(3), 645–654. https://doi.org/10.1002/jcp.21254

UniProt. (2022). UniProt Knowledgebase [Data set]. https://www.uniprot.org/uniprot/

Verzola, D., Picciotto, D., Saio, M., Aimasso, F., Bruzzone, F., Sukkar, S. G., Massarino, F., Esposito, P., Viazzi, F., & Garibotto, G. (2020). Low Protein Diets and Plant-Based Low Protein Diets: Do They Meet Protein Requirements of Patients with Chronic Kidney Disease?. *Nutrients*, *13*(1), 83. https://doi.org/10.3390/nu13010083

V'kovski, P., Kratzel, A., Steiner, S., Stalder, H., & Thiel, V. (2021). Coronavirus biology and replication: implications for SARS-CoV-2. *Nature Reviews. Microbiology*, *19*(3), 155–170. https://doi.org/10.1038/s41579–020-00468–6

Wamai, R. G., Hirsch, J. L., Van Damme, W., Alnwick, D., Bailey, R. C., Hodgins, S., Alam, U., & Anyona, M. (2021). What could explain the lower COVID-19 burden in Africa despite considerable circulation of the SARS-CoV-2 virus? *International Journal of Environmental Research and Public Health*, *18*(16), 8638. https://doi.org/10.3390/ijerph18168638

Weibel E. R. (2015). On the tricks alveolar epithelial cells play to make a good lung. *American journal of respiratory and critical care medicine*, *191*(5), 504–513. https://doi.org/10.1164/rccm.201409–1663OE

Wilkinson, D. J., Bukhari, S. S. I., Phillips, B. E., Limb, M. C., Cegielski, J., Brook, M. S., Rankin, D., Mitchell, W. K., Kobayashi, H., Williams, J. P., Lund, J., Greenhaff, P. L., Smith, K., & Atherton, P. J. (2018). Effects of leucine-enriched essential amino acid and whey protein bolus dosing upon skeletal muscle protein synthesis at rest and after exercise in older women. *Clinical Nutrition (Edinburgh, Scotland)*, *37*(6 Pt A), 2011–2021. https://doi.org/10.1016/j.clnu.2017.09.008

Worldometers. (2022). COVID-19 Coronavirus pandemic [Data set]. https://www.worldometers.info

Wu, G. (2016). Dietary protein intake and human health. *Food & Function*, (7), 1251–1265.

Wu, J., Zhao, M., Li, C., Zhang, Y., & Wang, D. W. (2021). The SARS-CoV-2 induced targeted amino acid profiling in patients at hospitalized and convalescent stage. *Bioscience Reports*, *41*(3), BSR20204201. https://doi.org/10.1042/BSR20204201

Yadav, R., Chaudhary, J. K., Jain, N., Chaudhary, P. K., Khanra, S., Dhamija, P., Sharma, A., Kumar, A., & Handu, S. (2021). Role of Structural and Non-Structural Proteins and Therapeutic Targets of SARS-CoV-2 for COVID-19. *Cells*, *10*(4), 821. https://doi.org/10.3390/cells10040821

Yamamoto, H., Kondo, K., Tanaka, T., Muramatsu, T., Yoshida, H., Imaizumi, A., Nagao, K., Noguchi, Y., & Miyano, H. (2016). Reference intervals for plasma-free amino acid in a Japanese population. *Annals of Clinical Biochemistry*, *53*(Pt 3), 357–364. https://doi.org/10.1177/0004563215583360

Yang, Y., Churchward-Venne, T. A., Burd, N. A., Breen, L., Tarnopolsky, M. A., & Phillips, S. M. (2012). Myofibrillar protein synthesis following ingestion of soy protein isolate at rest and after resistance exercise in elderly men. *Nutrition & Metabolism*, *9*(1), 57. https://doi.org/10.1186/1743–7075-9–57

Yapasert, R., Khaw-On, P., & Banjerdpongchai, R. (2021). Coronavirus infection-associated cell death signaling and potential therapeutic targets. *Molecules (Basel, Switzerland)*, *26*(24), 7459. https://doi.org/10.3390/molecules26247459

Yoshimoto, F. K. (2020). The Proteins of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2 or n-COV19), the Cause of COVID-19. *The Protein Journal*, *39*(3), 198–216. https://doi.org/10.1007/s10930–020-09901–4

SUPPLEMENT MATERIAL

Table S1

Relation between outcomes of COVID-19 and diet factors in countries Top-20 infection cases from different continents, January 31, 2022

Country	Cases			Consumed protein g/ person/day		
	Total Cases (mln)	Cases/ 1T population (RPr)	Deaths/1T population (IFR)	TP	AP	PP
World	378,903	48,6	0,73	81,2	32,1	49,1
USA	76,222	228,1	2,72	113,7	73,9	39,9
India	41,469	29,6	0,35	65,3	14,7	50,6
Brazil	25,454	118,4	2,92	90,9	52,8	38,1
France	19,140	292,2	2,00	112,1	69,7	42,4
UK	17,315	253,0	2,28	104,0	58,5	45,6
Russia	11,861	81,2	2,27	101,9	55,8	46,1
Turkey	11,619	135,5	1,02	101,2	35,8	65,4
Italy	10,983	182,1	2,43	106,8	57,0	49,7
Spain	9,961	212,9	2,00	107,1	66,5	40,6
Germany	9,896	117,5	1,41	104,2	63,1	41,1
Argentina	8,378	182,7	2,64	106,1	65,7	40,4
Iran	6,373	74,4	1,55	87,6	25,3	62,3
Colombia	5,887	113,8	2,60	72,4	37,2	35,2
Mexico	4,930	37,6	2,33	93,4	43,8	49,6
Poland	4,886	129,3	2,78	103,1	55,4	47,7
Netherlands	4,432	257,8	1,24	104,6	68,4	36,2
Indonesia	4,353	15,7	0,52	68,6	22,2	46,4
Ukraine	4,064	93,8	2,31	86,2	37,4	48,8
South Africa	3,605	59,6	1,57	83,4	34,9	48,8
Philippines	3,560	31,8	0,48	62,7	25,7	37,0

Correlation between rate of prevalence (RPr) or infection fatality rate (IFR) of the SARS-CoV-2 infection and amount of consumed animal protein (AP), plant protein (PP), total protein (TP). AP, PP, TP in g/day/person [38–39].

RPr = amount registered infected persons/1000 population (31.01.2022) [3], IFR= amount registered COVID-19 deaths/1000 population (31.01.2022).

Table S2

Correlation coefficients (r)

	RPr	IFR
IFR	0,41	
TP	0,79	0,57
AP	0,83	0,61
PP	-0,30	-0,24

Variation of correlation coefficients (r) between COVID-19 outcomes and consumed diet proteins. Pearson coefficients were calculated from data in Table 1.

Table S3

ID of HCoV Proteins from UniProtKB data base

Virus	Proteins		
	Pp1a	Pp1ab	Spike
SARS-CoV-2	P0DTC1	P0DTD1	P0DTC2
SARS-CoV	P0C6U2	P0C6X7-1	P59594
MERS-CoV	K9N638-1	K9N7C7	R9UQ53
HCoV-OC43	P0C6U7	P0C6X6	P36334
HCoV-HKU1	P0C6U3	A0A3G2KXK3	Q0ZME7